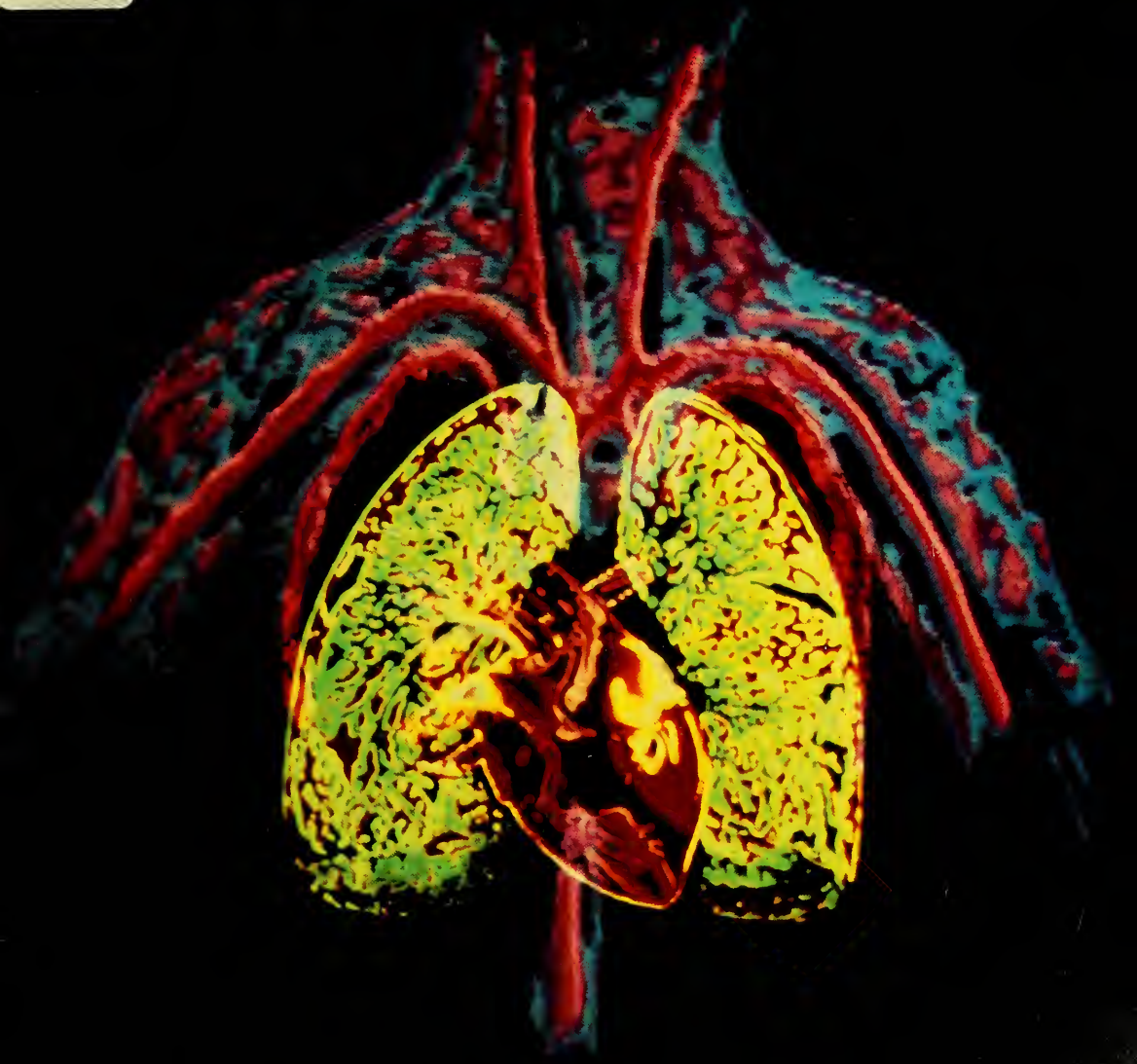
THIRTEENTH REPORT OF THE NATIONAL HEART, LUNG, AND BLOOD ADVISORY COUNCIL



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
National Institutes of Health

COVER ILLUSTRATION:
Image computer processed view of the heart, lungs and blood in the human body.

Thirteenth Report of the National Heart, Lung, and Blood Advisory Council

U.S. DEPARTMENT
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HUMAN SERVICES

Public Health Service
National Institutes
of Health

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung,
and Blood Institute
Bethesda, Maryland 20892

The President
The White House
Washington, D.C.

Dear Mr. President:

In accordance with Public Law 95-622, we take great pleasure in submitting to you, and to the Congress, our thirteenth annual report. This report describes the progress of the National, Heart, Lung, and Blood Institute's efforts during the past year to control and prevent diseases of the heart, lungs, and blood as well as to ensure an adequate and safe supply of blood resources.

As we forward this report, we would like to express our gratitude for the opportunity of serving you, the Congress, the Institute, and the people of our Nation, all of whom benefit from the programs that the Institute sponsors.

Respectfully,

The National Heart, Lung,
and Blood Advisory Council

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CONTENTS

INTRODUCTION

In this report the National Heart, Lung, and Blood Advisory Council has focused on the importance of basic research to the Institute's efforts to accomplish its mission. The advances described here include both innovative concepts and techniques in basic research and also certain clinical applications made possible, to a large degree, through the work of biomedical scientists.

The first part of the report describes some of the most significant developments related to the cause, prevention, diagnosis, and treatment of heart, vascular, lung, and blood diseases, as well as to blood resources. In addition, some highlights of current population-based studies are given. The report then mentions certain Institute priorities for the immediate future. These include increased emphasis on Specialized Centers of Research; on technological innovations to improve the health of the Nation from the partnership between the National Institutes of Health and commercial organizations, through the Small Business Innovation Research Program; on career development of new investigators in biomedical research, especially physician scientists and minority scientists; and on construction or renovation of our Nation's research facilities. Finally, the Council recommends a budget that would enable the Institute to carry out a balanced and diverse program of biomedical research, training, demonstration, and education.

As shown in this report, considerable progress has been made in the Institute's struggle to reduce and possibly even eliminate some of the heart, vascular, lung, and blood diseases as well as ensure an adequate and safe supply of blood resources. But so much more remains to be accomplished. Diseases of the heart and blood vessels are still first in the list of causes of death in the United States, and lung and blood diseases continue to strike down far too many American people. This is an age of great progress and promise in biomedical research. With adequate financial support, the progress can continue. With sufficient funds, the promise of a healthier Nation can become reality.

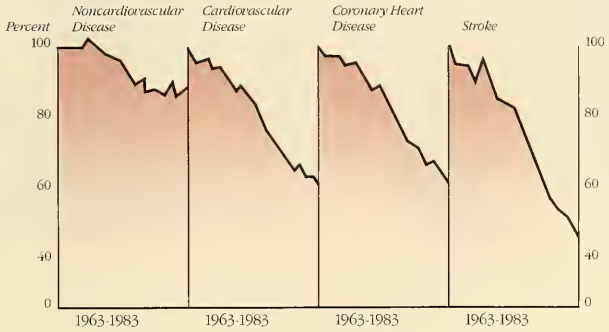
Heart and Vascular Diseases

Perhaps the most striking evidence of Institute accomplishments over the years is the significant decline in mortality rate from cardiovascular diseases. In the past 20 years, the mortality rate from coronary heart disease has decreased 39 percent and that from stroke 55 percent. This decline can be attributed to wider adoption of preventive efforts to reduce risk factors, to improved diagnosis and treatment, as well as to an improved understanding of the basic mechanisms that lead to the development of atherosclerosis.

While the decline in the death rate from cardiovascular diseases is a source of satisfacation, it is no cause for complacency. The magnitude of the problem is still tremendous. Each day an estimated 3,400 Americans—more than 2 a minute—suffer a heart attack. An estimated 60 million Americans—almost one-quarter of the U.S. population—have hypertension, a major risk factor for heart attack and stroke. Every year, coronary heart disease is responsible for more than 550,000 deaths in the United States.

The advances in basic and applied research, some of which are described in the following sections, are impressive. But clearly these advances are just the beginning of the journey towards the goal of the reduction and possible eradication of heart and vascular diseases.

20-Year Trend in Cardiovascular and Noncardiovascular Death Rates as a Percent of Rates in 1963, U.S.*



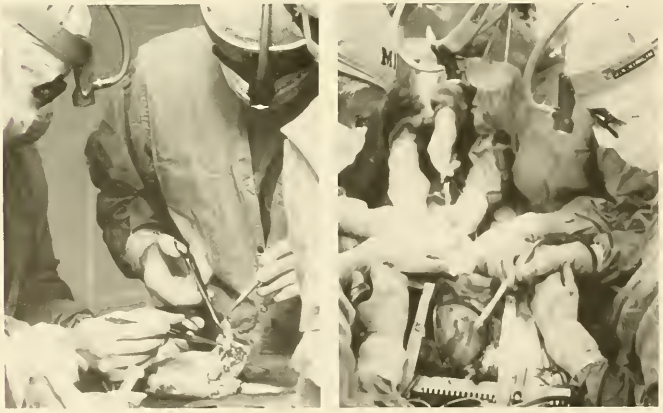
* *Age-adjusted*
Source: *Vital Statistics of the U.S., NCHS*

Transplantation Developments

The last few years have seen a rapid rise in the number of heart transplantations performed in the world and in the number of institutions performing them. In addition, approximately 30 patients suffering from advanced forms of noninfective lung disease and associated heart disorders have had transplantation of both the heart and lungs as a unit.

The clinical feasibility of combined heart and lung transplantation has become more promising with the advent of the new suppressive agent, cyclosporin. Healing has been good at the sites where the transplanted organs are attached to the patient, and survival rates have been improving. But while infectious complications have been markedly reduced since the use of cyclosporin and low-dose steriods, frequent side effects that require treatment, such as dysfunction and progressive airflow obstruction, show the need for further improvement in immunosuppressive techniques.

Another interesting research development in the field is with heart and liver transplantation. While both heart and liver transplantations have been successfully performed individually for a number of years, only recently in several patients have both organs been transplanted simultaneously. A particularly exciting application of such double transplantation took place in 1984, when a 6-year-old girl received both a heart and liver from the same donor. The girl was suffering from familial hypercholesterolemia, a congenital defect causing severe elevation of her blood cholesterol and premature hardening of the arteries. Although only 6 years old, she had already suffered a heart attack and had undergone open-heart operations to bypass her clogged coronary arteries. After her successful double organ transplants, her blood cholesterol levels fell by 81 percent as her new liver was now able to remove cholesterol from her blood at a nearly normal rate. Basic research in molecular genetics identified this patient's underlying problem, while advances in immunology and transplantation techniques combined to give hope of a relatively normal life to this young girl with an otherwise fatal disease.



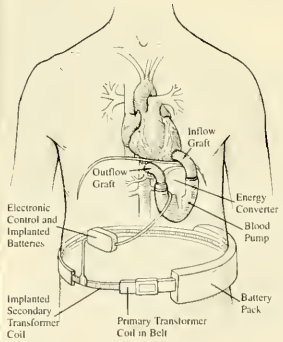
Young girl after a successful heart and liver transplantation to correct a congenital defect that had caused severe elevation of her blood cholesterol level and premature hardening of her arteries. Now she has a chance to lead a relatively normal life.

Heart Assist Devices

During the past year, at least two cardiac transplantation centers successfully employed mechanical heart assist devices to keep alive cardiac transplant candidates, who had developed circulatory collapse because of heart failure, until a suitable human heart was available for transplantation. These mechananical units, called ventricular assist devices, are either electronically or air-driven units designed to perform all of the heart work in patients with terminal heart disease. Once in place adjacent to the patient's own heart, the assist device beats in harmony with the rest of the heart. The assist device bypasses blood from the patient's damaged ventricle and pumps it into the aorta for adequate circulation to all body organs.

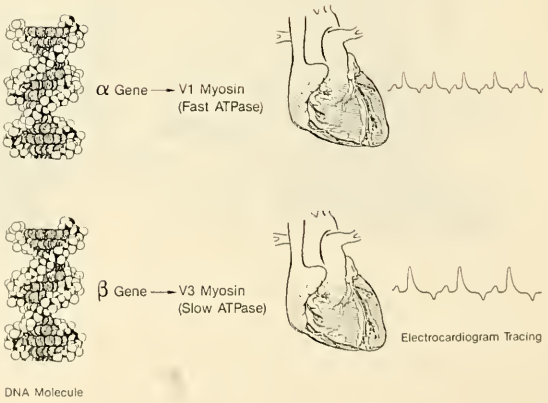
Besides buying time for heart recipients in need of a donor organ, the assist devices have potential use in the 1 to 3 percent of heart surgery patients who cannot be weaned successfully from heart-lung machines at the end of open-heart surgery. The temporary use of such devices also will probably supply information about the effects of permanent mechanical hearts, which may lead to the successful use of such devices in patients with end-stage heart disease.

The electronically powered assist device is the prototype of the future, where all the components of the assist system will be implanted, and power will be supplied from batteries worn in a vest to the implanted pump through the skin using an air-coupled transformer. Researchers are evaluating the safety, efficacy, and reliability of these devices in carefully planned laboratory and animal studies.



• *Design for a future, electronically-powered heart assist device. All the components would be placed inside the body, and power would be supplied from batteries worn in a vest.*

• *Different forms of ventricular myosin, a protein that affects the heart's performance as a pump. When the alpha gene in the DNA molecule is switched on, myosin V-1 increases, which increases the rate of muscle contraction. When the beta gene is switched on, myosin V-3 increases, decreasing the rate of muscle contraction. Regulation of these forms of myosin may one day provide a way to treat heart disease.*



Contractile Proteins of the Heart

With the problem of organ donor availability and the need for improved immunosuppressive techniques, transplantation and heart assist devices are unlikely to be used to treat more than a small percentage of desperately ill patients with heart disease. Researchers are, therefore, striving to better understand the biological phenomena leading to hypertrophied (enlarged) and failing hearts.

Since cardiac contraction and, hence, the heart's performance as a pump depends primarily on the interaction of the myocardial contractile proteins, investigators have suggested that a defect in one or more of these proteins may often be involved in heart failure.

Research thus far has focused on myosin, the contractile protein molecule that is central to the function of all muscle. Myosin produces muscle contractions by converting the chemical energy stored in a compound called ATP into physical energy or movement. How fast a muscle contracts depends on its ATPase activity, that is, on the rate at which myosin uses ATP. In a pioneering study done in 1962, investigators found that myosin from hypertrophied and failing hearts had dramatically reduced ATPase activity.

Upon searching for the molecular basis of the change in myosin ATPase activity, researchers made the somewhat startling discovery that heart ventricular muscle contained not one but three structurally different forms of myosin. Named ventricular myosin-1, -2, and -3 (V-1, V-2, V-3), these also differ in their ATPase activity; myosin V-3 has a lower ATPase activity, and therefore a lower rate of contraction, while myosin V-1 has a higher ATPase activity and a higher rate of contraction.

Furthermore, the myosin composition of the heart changes as a result of developmental, physiological, and pathophysiological factors. For example, in the rabbit, myosin V-1 diminishes as the animal matures, from 50 percent at approximately 4 weeks of age to 10 percent at approximately 12 weeks, while the level of myosin V-3 increases from 50 percent to 90 percent during this period. Another example is the effect of thyroid hormones on the myosin composition of the heart. Specifically, when thyroid hormone is administered to adult rabbits, myosin V-3 decreases from 90 percent to 10 percent, while myosin V-1 increases from 10 percent to 90 percent. This changing or switching of myosin forms is being thoroughly studied. Researchers have pinpointed the genes coding for the different forms of myosin, the alpha and beta genes, which are extremely close to each other on the DNA molecule. In fact, the alpha and beta genes are the closest yet discovered in man or in any other mammal. When the alpha gene is switched on, myosin V-1 increases, which increases the rate of muscle contraction. When the beta gene is switched, on, myosin V-3 increases, decreasing the rate of muscle contraction. Researchers are actively searching to find the portion of the DNA molecule that controls the expression of the alpha and beta genes.

These results suggest some novel possibilities for therapeutic strategies. Although incompletely resolved and an area requiring more research, the adult human ventricle appears to consist mainly of V-3, the low ATPase form of myosin. Therefore, the human heart has the potential for "up-regulation"—that is, a switch from the low activity form of myosin to the high activity form—and this might serve to improve the pumping effectiveness of hypertrophied and failing hearts. Even though this research is still in its infancy, the regulation of the expression of myosin V-1 and V-3 may one day provide a rationale for treating heart disease.

ANF and the Regulation of Blood Pressure

In the cardiovascular disease program, the control of blood pressure is coming under increasingly intense scrutiny. Although complex, and involving multiple regulating mechanisms, it is now clear that one important component is atrial natriuretic factor (ANF), a hormone first identified in the 1980's. We now know that this hormone comes from some very small particles in cells from the upper chambers of the heart (the atria). For decades, scientists have observed these particles under the microscope but their function was unknown.

ANF acts to promote kidney function, relax smooth muscle, and lower blood pressure, activities that have become associated with this hormone only very recently. This knowledge has been acquired following the application of modern techniques of cellular and molecular biology, using recombinant DNA, monoclonal antibodies, and x-ray crystallography. The result has been the isolation and purification of ANF and the cloning of the gene responsible for its synthesis. In addition, the amino acid sequence of the ANF precursor has been determined, and a variety of smaller active compounds called peptides have been identified and sequenced. Based on preliminary studies, the fall in blood pressure associated with ANF is attributable to several factors, including smooth muscle relaxation and the inhibition of the secretion of renin from the kidneys.

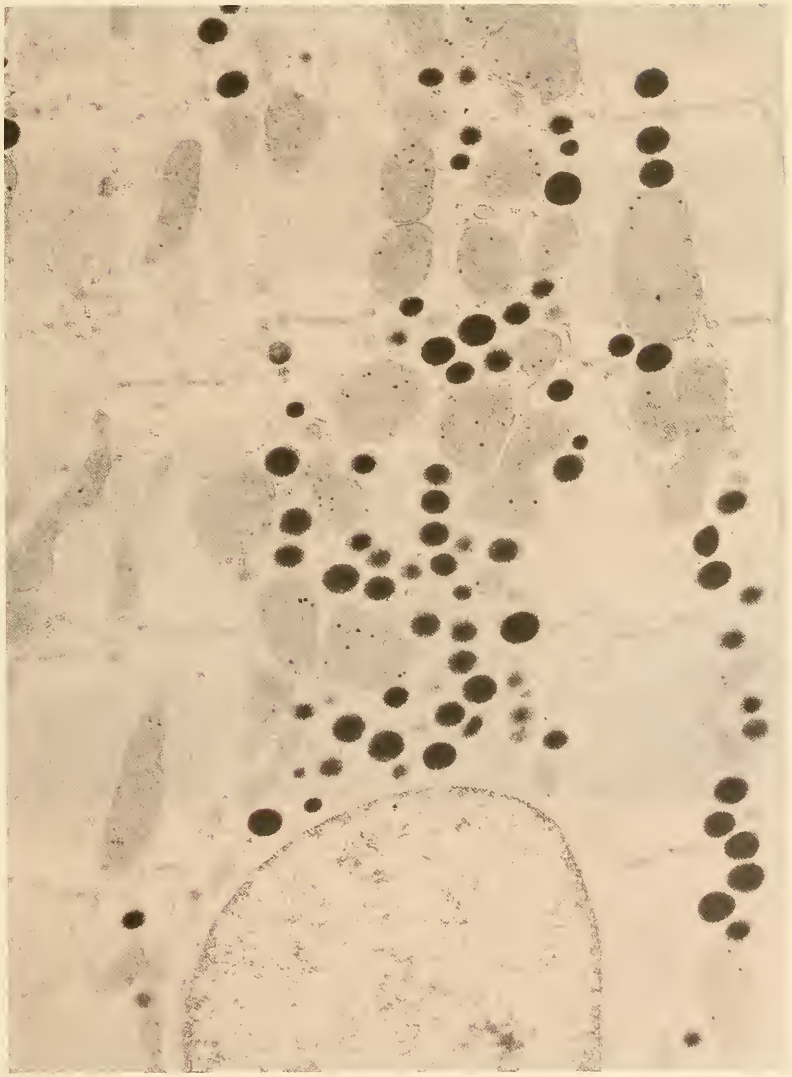
With the ability to clone the gene, ANF can now be synthesized in quantity, thus making it feasible to determine what role the hormone may play in a variety of cardiovascular diseases, including hypertension.

Echocardiography

Over the past 10 years, ultrasound has developed to the point where it is now a routine part of the examination of patients with suspected or known cardiovascular disease. The first echocardiograms, known as M-mode echocardiograms, were done with a single transducer in one dimension. Subsequently, the technology evolved until two-dimensional or moving pictures of the heart could be obtained with ultrasound.

Recently, the returning ultrasound signal has been processed to extract information about flow velocity using the Doppler principle. With this technique, it is possible to measure blood flow within the major chambers of the heart noninvasively, to detect the leaking of cardiac valves, and to determine the severity of valve narrowing. The newest development has extended the use of the Doppler method into cardiac imaging. With this method, known as color flow mapping, one can obtain moving pictures of blood flow within the heart. This method of color flow mapping represents a significant advance in the ability to identify and quantify noninvasively the severity of leaking heart valves.

Atrial granules (black substances) in the rat heart. Atrial natriuretic factor, which is a hormone from such granules in certain human heart muscle cells, acts to promote kidney function, relax smooth muscle, and lower blood pressure (original magnification ×18,600).



Digital Subtraction Angiography

Cardiac digital subtraction angiography involves processing x-ray images of the heart using digital computers. With a digital computer (one that translates pictures into numbers), cardiac digital subtraction angiography subtracts a preinjection x-ray image, called a mask, from later shots of the heart after a contrast medium has been injected through a peripheral vein or artery. The computer processing allows information to be extracted that may not be available when the angiograms are recorded onto film.

The technique of cardiac digital subtraction angiography is being used to obtain images of the left ventricle (the major pumping chamber of the heart) during routine cardiac catheterization. The advantage of the method is that images can be obtained with one-fourth the amount of injected dye used with conventional methods. Therefore, this allows repeated studies to be performed at the time of catheterization to determine if the function of the heart has deteriorated during stress.

X-ray images of the blood vessels supplying the heart with blood, known as coronary angiograms, can also be processed by digital subtraction techniques. Currently, intra-arterial injection of contrast material is needed. The ability to process these images with a computer provides a convenient method to measure the severity of narrowing of the blood vessels using a smaller catheter and less contrast material then needed in conventional angiography.

Digital subtraction angiography is also useful as an adjunct to coronary angioplasty. This latter technique involves inflating and deflating balloons inside narrowed blood vessels in order to widen the vessel and improve blood flow. By using computer-processed x-ray images of the blood vessels, physicians can more conveniently position the balloons inside the arteries prior to inflation and deflation.

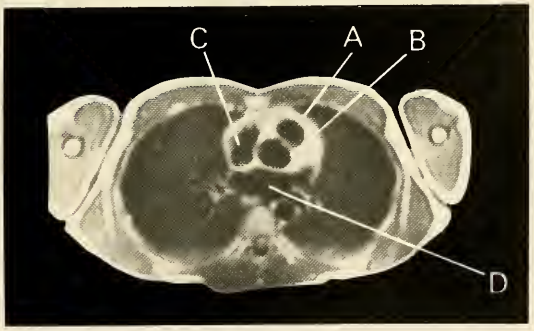
Thus, digital subtraction angiography has evolved as a useful technique to process x-ray images that are obtained during routine heart catheterization. Digital subtraction angiography, in conjunction with other intravenously or arterially injected contrast material, is currently used clinically in many centers instead of conventional angiography to evaluate the presence and severity of lesions in coronary arteries as well as in carotid, femoral, abdominal, renal, and intracerebral arteries. The procedure is often performed on an outpatient basis.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI), which relies on forming images based on resonance characteristics of selected nuclei, began some 40 years ago in experiments performed by physicists. The discovery of separate resonance lines for chemically different hydrogens in alcohols shifted interest in this technique from physics to chemistry, where it remained until recently. Then, the realization that magnetic resonance signals could be obtained from intact tissue attracted clinicians to the diagnostic possibilities of this technique in the human body. Research to date has shown that MRI can delineate a variety of physiologic and pathophysiologic processes in intact organs and organisms. The development of MRI technology for use in biomedical research and diagnosis is a collaborative effort involving basic scientists and clinicians.

The essential components of an MRI system are a magnet and a radio-frequency transmitter and receiver. The size of the magnet and its magnetic field strength are among the important factors that determine the type of information that can be obtained. For instance, researchers working with large bore magnets have studied *in vivo* metabolism in humans.

In contrast to other currently applied whole body imaging processes, the procedure is minimally invasive and the subject does not receive ionizing radiation. High quality images may be obtained of many internal structures within the body, including the heart, liver, pancreas, and brain. Different characteristics of the body, such as moving blood and fat content, can be studied. MRI also can be used to obtain metabolic information by tagging intravenously administered isotopes to image phosphorus or oxygen rather than the standard hydrogen ion. Approximately 160 whole body magnetic resonance imagers exist throughout the world, and many scientists are convinced that the technique will replace conventional computerized tomography. Although MRI is still in its infancy, the combination of three-dimensional imaging without ionizing radiation and the potential to evaluate metabolic and tissue function make MRI one of the most exciting medical technology developments in recent years.



Magnetic resonance image. This cross-sectional view shows the lungs (dark areas) on either side of the heart. In the heart, the pulmonary artery (A), aorta (B), right atrium (C), and the left atrium (D), are clearly seen.

Through the many programs managed by the Institute, there has been considerable progress towards solving the clinical problems posed by diseases of the lungs. Both in pediatric and adult patients, lung diseases can be broadly divided into those affecting conducting airways and those affecting the supporting structure or interstitium. The pathways by which interstitial diseases are produced are not yet fully understood, and their intricacy requires the application of sophisticated techniques in basic research for their resolution.

This section is directed to progress made and continuing in several areas related to interstitial lung diseases, and with it the expectation of more specific and effective patient care. For example, the lack of accessibility of vital tissue in diseased lungs has made research difficult. This difficulty, however, has been overcome in a number of ways, including the development of experimental models and the use of bronchoalveolar lavage, which is a method of obtaining lung cells and fluids by bathing or washing airways and air sacs with a liquid that is retrieved. In another area, the now widely held concept of alveolitis as an inflammatory process in small airspaces implies that adjacent interstitial structures are also involved. Such changes occur in the adult respiratory distress syndrome (ARDS), in which damaged capillaries permit leakage of fluid into the interstitium and alveoli, and in the initial stages of chronic interstitial pulmonary fibrosis (execessive amounts of fibrous tissue and scarring). Animal models have been developed for laboratory studies, in which the pulmonary edema of some forms of acute lung injury can be produced. In selected circumstances they may later progress to pulmonary fibrosis. Both of these forms of lung damage are similar to the human variety. The development of models of this kind has made possible observations that have added greatly to our understanding of the abnormal processes involved and have potential clinical relevance.

Bronchoalveolar Lavage

Within the past decade, bronchoalveolar lavage (BAL) has been used in humans in combination with fiberoptic bronchoscopy to obtain washings from small airspaces. Previously, the only methods available for tissue sampling depended on various forms of lung biopsy. With BAL, the cellular and chemical contents of the washings reflect inflammatory changes present at that level and in the adjacent parenchyma, and have been used to separate and identify various types of interstitial lung disease.

Accumulated experience with this relatively noninvasive method of sampling from deep in the lung substance has proved it to be safe, and it has gained wide acceptance. Up to the present, however, its diagnostic value has been limited because of considerable overlap in reported findings and the absence of adequate markers of disease. A great deal of work is in progress to identify specific cellular and soluble markers of lung damage in various conditions, which could make it possible to separate and manage the many different types of interstitial lung disease more effectively and to follow their progress and response to therapy.

In spite of present limitations, much important information has accumulated from its use. One example is with sarcoidosis, which is a granulomatous disease of the lung interstitium that may progress to fibrosis. In sarcoidosis, the major immunoregulatory cell in BAL effluent is a cell called the T-lymphocyte, an important participant in chronic inflammatory reactions, whose number has been found to decrease with improvement of the disease. Although relatively common, sarcoidosis is not well understood. With increased experience, these findings should provide an index of response to treatment as well as an improved understanding of the natural history of the condition, both of which are important to its proper management.

The technique is also being used with workers exposed to fibrogenic dusts, such as asbestos and silica, to assess the effect of past and current dust inhalation on their lungs. This method measures lung exposure more directly than does environmental sampling at the worksite, although the latter has provided the reference values up to the present time. Measurements of this kind will make it possible to compare the dust content in the lungs of healthy workers with that in the lungs of workers with clinical pulmonary silicosis who have been exposed to the same environment. The results of these studies should permit assessment of the effects of different levels of silica and asbestos lung dust over varying periods of time. Based on these findings, improved protection can be developed for workers exposed to these potentially harmful substances.

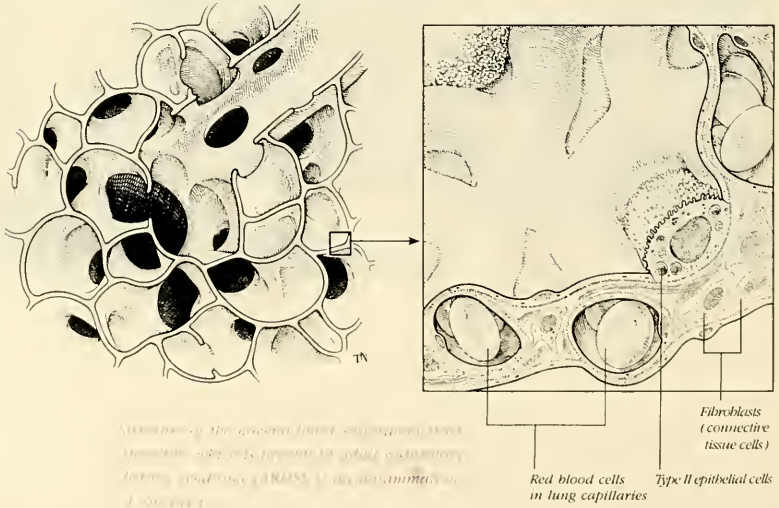
Worker handling potentially harmful substances. Bronchoalveolar lavage is being used to assess the effect of dust inhalation on such worker's lungs.

Adult Respiratory Distress Syndrome

The alveolitis (inflammatory process in the small airspaces) present in ARDS is similar to that in the early stages of chronic interstitial fibrosis of various kinds, but is much more intense in degree. This form of high protein, noncardiogenic pulmonary edema is due to leakage of fluid from damaged capillaries into the interstitium and alveoli of the lung. The outcome is fatal in more than half of those afflicted despite the skilled application of advanced technology to patient care. ARDS may also complicate a wide variety of clinical conditions ranging from diffuse pneumonia to trauma, shock, and sepsis (a condition where disease causing organisms or their toxins are present in blood or tissue). Because of the high death rate and widespread occurrence of ARDS, it is of major importance to better understand the mechanisms of tissue damage that occur so that properly directed interventions can be undertaken.

One area of study has been the complement system. This system is an important part of the body defense mechanisms in acute inflammation and may be activated by both immune and nonimmune stimuli. Early evidence indicated that the complement system might be critical in the initiation of events leading to the tissue damage of ARDS, particularly by attracting neutrophilic leukocytes (certain white blood cells) to the lungs. However, more recent work has shown that biologic and immunologic assays of intravascular complement activation, which are often positive in patients with sepsis, neither correlate with the initial severity of the clinical condition nor predict the development or progression of associated lung injury. It now appears that in patients with sepsis, these assays have little relevance to lung injury, and that efforts directed to combating activation of complement may be of doubtful value. Consequently, the role of activated complement in attracting leukocytes to the lungs of these patients also needs more critical scrutiny. The present findings are important in redirecting efforts to combat ARDS in septic patients along different lines of investigation from those that have been emphasized in the past, particularly since they have not resulted in a solution to the problem.

Another area of study involves arachidonic acid, which is a fatty acid released by enzymes from cell membranes as a result of stimulation by a large number of mediators. Its many metabolic derivatives have important roles in inflammation, including constriction of small airways, changes in caliber of small blood vessels, increased vascular permeability, and enhanced leukocyte infiltration. From animal studies, researchers have



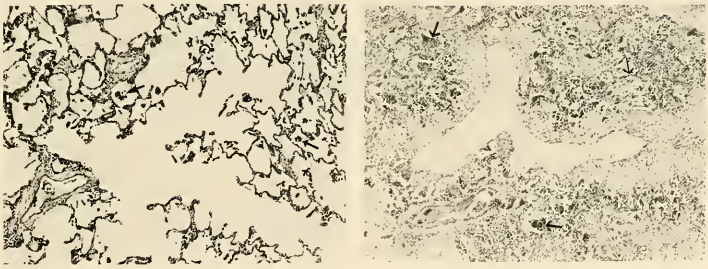
found that these chemical substances are released from the lungs during acute pulmonary injury, and the development of alveolitis is believed to be influenced by them.

One harmful effect attributed to arachidonic acid metabolites is interference with the protective constriction of small blood vessels, which directs blood to better ventilated areas of injured lungs. The absence of this beneficial mechanism can result in aggravation of the severe hypoxemia (lack of oxygen in the blood) found in ARDS and make treatment of impaired arterial blood oxygenation more difficult. Drugs that interfere with the production of arachidonic acid metabolites reduce the damage caused by them in experimental animals, including constriction of small blood vessels and airways.

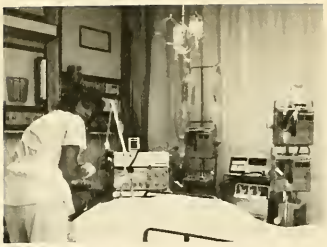
From observations of this kind, a growing appreciation of the underlying mechanisms in this severe form of respiratory failure may lead to the development and use of pharmacologic agents capable of acting more efficiently on arachidonic acid pathways. The ability to improve the relative distribution of blood flow and ventilation would greatly improve the outlook of patients with acute lung injury of this kind.

In ARDS and in advanced chronic interstitial pulmonary fibrosis, there is severe impairment of transfer of oxygen from the alveoli to the blood stream resulting in hypoxemia. High concentrations of inspired oxygen are, therefore, needed to maintain arterial oxygen at life-supporting levels. However, the inhaled concentrations that are needed may be toxic to lung tissue and produce damage similar in microscopic appearance to that of ARDS. The occurrence or worsening of severe pulmonary fibrosis as a frequently fatal consequence of oxygen toxicity is a complication of treatment that necessitates still higher levels of inspired oxygen.

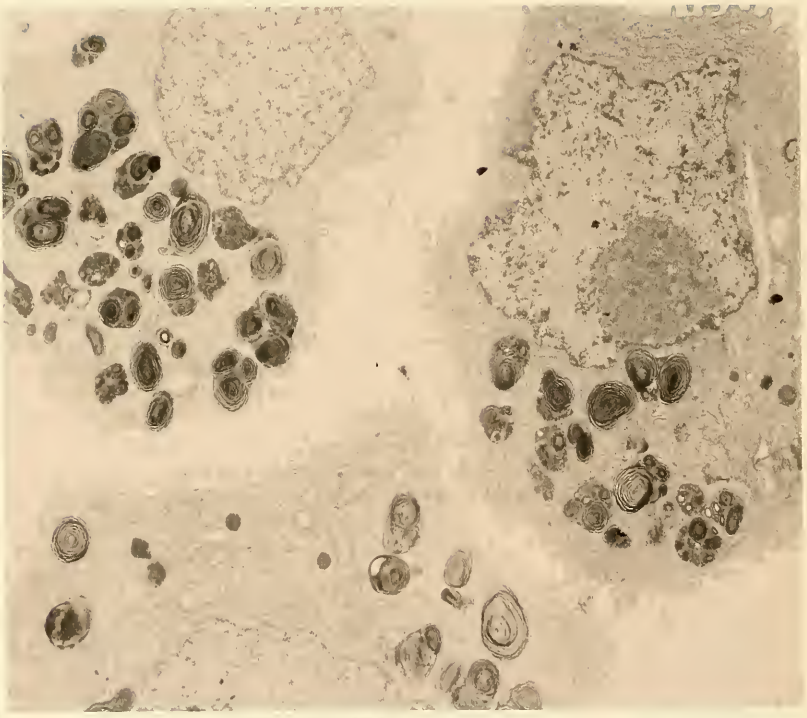
Patients with ARDS require support by mechanical ventilation and can receive only limited nutrition. Since oral feeding is not possible, nutrition is often received intravenously resulting in variations in caloric and protein intake. Studies in animals have doucumented that a limited protein diet increases the toxicity of oxygen to the lungs, but this can be prevented or reduced by supplementation with sulfur-containing amino acids. Researchers believe that restriction of protein is associated with a failure to increase glutathione, a substance which protects cells against oxidant-induced injury. Better protection from this form of lung damage is needed for seriously ill patients who require high levels of inspired oxygen to maintain life during the time necessary for the lungs to heal. These observations are important in directing attention to adequate and specific



Pathology of ARDS. This picture on the left is of a normal lung with three alveolar ducts (white branching pattern). The arrow shows occasional groups of macrophages in the alveolar spaces. The picture on the right shows an alveolar duct (white) in an ARDS patient. The duct is lined by a layer of fibrosis (excessive amounts of fibrous tissue and scarring), and the air spaces are reduced. There are also increased numbers of macrophages (arrows).



Hospital setting for patients afflicted with ARDS.



Transmission electron micrograph of the more metabolically active type II pneumocytes (type cells of the alveoli in ARDS syndrome, magnification x 9,000).

protein intake in ARDS, particularly during oxygen supplementation.

Collapse of terminal airspaces, or microatelectasis, is a prominent feature of ARDS. Blood that continues to flow through these areas lacks adequate oxygen, leading to hypoxemia. The thin, type I-lining cells of the alveoli are severely damaged in this condition and are replaced by increasing numbers of more metabolically active type II cells. The latter synthesize surfactant whose properties prevent microatelectasis in normal lungs. It has recently been shown that after acute lung injury in experimental animals, the surfactant produced by reparative type II cells lacks its normal ability to lower surface tension and prevent collapse of terminal airspaces. This has important clinical implications, since mechanical means to preserve patency of alveoli in ARDS and thereby improve levels of arterial blood oxygen may not be successful.

A clinical trial is being planned to evaluate the use of a synthetic surfactant in neonates suffering from the infant respiratory distress syndrome, in which microatelectasis is the main contributor to life-threatening hypoxemia. Obvious differences exist between the previously undamaged lungs of these usually premature infants, in whom surfactant is deficient because of immaturity, and the damaged lungs of the adult form, in which an underlying disease process exists that may interfere with its synthesis and function. Nevertheless, there is a need to explore the possibility of reducing the high mortality rate of ARDS by improving surfactant function. Future work will determine the feasibility of this approach.

Interstitial Pulmonary Fibrosis

Interstitial pulmonary fibrosis is characterized by initial inflammation followed by obliteration of small airspaces and blood vessels from excessive or irregular deposits of collagen fibers in the lungs. A large number of occupational and environmental inhalants can produce these changes, notably silica and asbestos. Similarly, numerous drugs and toxins in general use, such as bleomycin and nitrofurantoin, as well as viral and other pulmonary infections can cause this form of pulmonary damage. There remains a large group of unknown causes, including sarcoidosis and idiopathic pulmonary fibrosis, with individual characteristics enabling them to be diagnosed separately from each other but with the common feature of interstitial pulmonary fibrosis. The frequent result in all of these diseases is severe limitation of lung function, with small stiff lungs and impaired transfer of oxygen into the bloodstream, leading to permanent disability and death.

Alveolitis is present in the initial stages whatever the cause, and the more sustained inflammatory changes of lung parenchyma are descriptively known as chronic interstitial pneumonitis. Several types of chronic inflammatory cells participate in these prefibrotic changes. Prominent among them are lymphocytes of the immune system, which have a defensive and regulatory function. They stimulate macrophages to produce a large number of substances influencing and occasionally damaging adjacent tissue. Along with other factors, lymphocytes and macrophages induce fibroblasts to produce large amounts of collagen with eventual scarring and loss of function in the affected area. The complexity of these cellular and extracellular interactions has made their elucidation difficult, and without this knowledge, patient treatment is often ineffective. A great deal of investigation has been directed toward finding a solution for these problems.

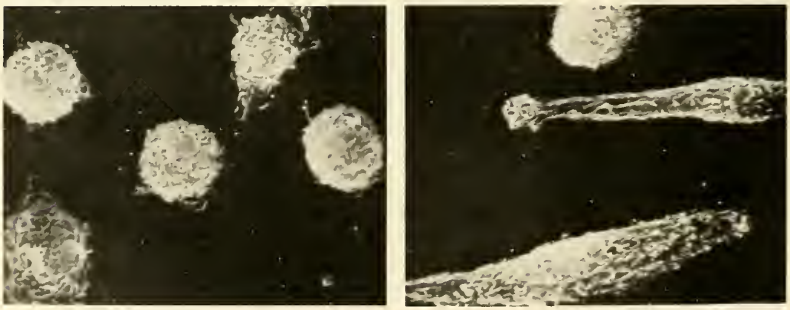
The alveolar macrophage has its origin in blood monocytes, and appears early in lung inflammation to carry out scavenging and secretory functions under either immune or nonimmume direction. Researchers have found that in some animals, immune markers appear on the cell surface as it ages. The identifying antigen has not been found elsewhere in the body and appears to be specific for these normally protective cells of the

lower respiratory tract and interstitium. The relationship between the emergence of this marker and altered function in the alveolar macrophage needs to be clarified. In the future, it should be possible to identify specific macrophages in this way and eventually reduce, by immune modulation, some of their damaging effects. This would be of great potential benefit in controlling inflammatory disease of the interstitium and subsequent fibrosis.

Of the many substances produced by macrophages, several influence the formation as well as the dissolution of blood clots, and also take part in the inflammatory process. Fibrin, for example, is important in anchoring fibroblasts where inflammation is present. A correlation exists between the amount of fibrin deposited in the lung interstitium and the subsequent localization of fibrosis there. In patients with sarcoidosis, fibrin accumulates in areas with a large number of macrophages. Apparently, fibrin deposition precedes the appearance of fibrosis in the lungs of patients with this disease and could become useful as a marker for indicating the risk of its development. Methods for protecting the lungs in these circumstances could then be better timed and directed.

Collagen, another substance, is the most common protein in the body and provides the normal extracellular framework by which its structure is supported. Produced by fibroblasts, collagen is the main constituent of scar tissue throughout the body and the principal component of interstitial pulmonary fibrosis.

Much attention has been given to developing pharmacologic agents that might influence collagen production or formation. Its considerable strength comes from chemical cross-linking, which takes place during synthesis. In animal models of pulmonary fibrosis, cross-linking can be prevented by blocking the catalytic enzyme lysyl oxidase. As a consequence, the stiffness usually associated with this condition does not develop. Indeed, when collagen synthesis is blocked in experimental animals, which are then given cadmium chloride into the trachea, the changes produced are those of emphysema, a condition of reduced lung elasticity, rather than the fibrosis that usually results from administration of this chemical substance. This observation has led to speculation that changes in collagen formation are involved in both these important human diseases, and strengthened the belief that methods for its control should be of primary concern in their management.



Another approach substitutes analogues for the two major constituents of the collagen molecule, proline and hydroxyproline. When the analogues were given to experimental animals, the development of pulmonary fibrosis was interfered with, and the inflammatory reaction to oxygen toxicity was reduced. Although a number of problems remain to be solved, including specificity of action, these findings open promising avenues of approach to controlling this serious form of lung disease.

To the present, conventional therapy has involved the use of adrenal corticosteroid drugs, which inhibit the production of collagen by fibroblasts. But their success has been poor in slowing the development of fibrosis, and their long-term use is associated with serious side effects, particularly suppression of immune defenses and the development of osteoporosis. Experiments in animals have shown that the inhibitory effect is peculiar to collagen peptide synthesis rather than suppression of total cellular protein production, as might be expected from other consequences of their use. This valuable insight into the mechanism of their action has potential for the development of drugs that can produce this particular effect without the other undesirable side effects of steroid therapy.

Lung Transplantation

Pharmacologic therapy has had only moderate success in combating immune and nonimmune diseases of the lung interstitium. Consequently, a significant number of patients become totally disabled and eventually die. The end stage fibrotic lung is capable of only minimum function, and since the process can not be reversed, lung transplantation remains a possible option when no other disease process is present. This procedure has been shown to be technically feasible both in experimental animals and in man. As with other transplantation procedures, a major obstacle has been the rejection of the donor lung by the body's immune system. Previously available methods for dealing with this problem have depended on corticosteroid and immunosuppressive agents and roentgen therapy. These have had variable success, and their long-term use has been associated with unwanted complications including the development of lymphoid malignancies. In recent years, cyclosporine has proved to be helpful in preventing rejection of kidney, liver, and heart and lung transplants. Its more widespread availability offers a valuable tool in the management of end-stage pulmonary fibrosis by facilitating combined cardiopulmonary replacement. Its value in controlling immune mediated pulmonary fibrosis remains to be explored.

The widespread occurrence of interstitial lung diseases in medical and surgical practice and through industrial and environmental exposures makes them a matter of concern in health care. Advances in our understanding of the mechanisms involved in their production have brought greatly improved expectation of therapeutic answers and prevention, but a great deal more work is needed to refine this new knowledge for the patient's benefit.

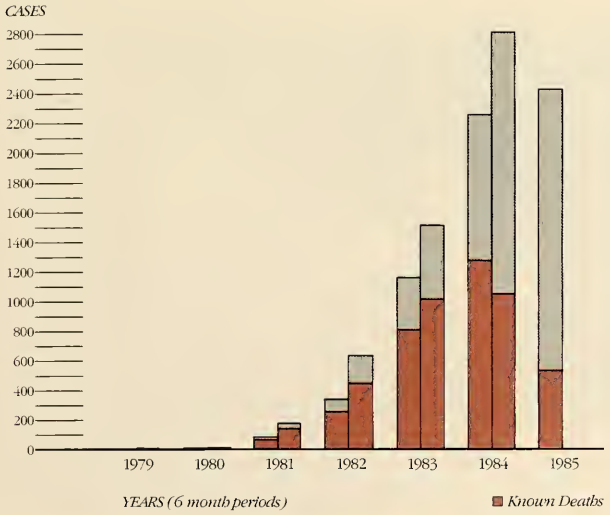
Blood Diseases and Resources

The Institute continues to manage a balanced program for research and research training in blood diseases and resources. Although the planning and projects of this program are extensive and worthy of detailed discussion, this brief report will be confined to several areas of particular interest to the Council and the biomedical research community. These areas include acquired immune deficiency syndrome (AIDS), sickle cell disease, thrombosis (blood clotting), and plans for increased efficiency in managing the Nation's blood resources through improvements in the field of transfusion medicine.

Acquired Immune Deficiency Syndrome

AIDS was first identified as a disease complex in 1981. Since then, it has received considerable attention in the medical literature and in the lay press. AIDS is characterized by a severe depression of the body's immune system, resulting in susceptibility to many otherwise harmless infectious agents as well as to certain malignancies. At present, AIDS has a mortality of about 50 percent, with indications that this level will probably increase. Over 11,500 cases of AIDS had been reported as of July 1985.

Aids Cases and Known Deaths
United States, 1981-July 1985



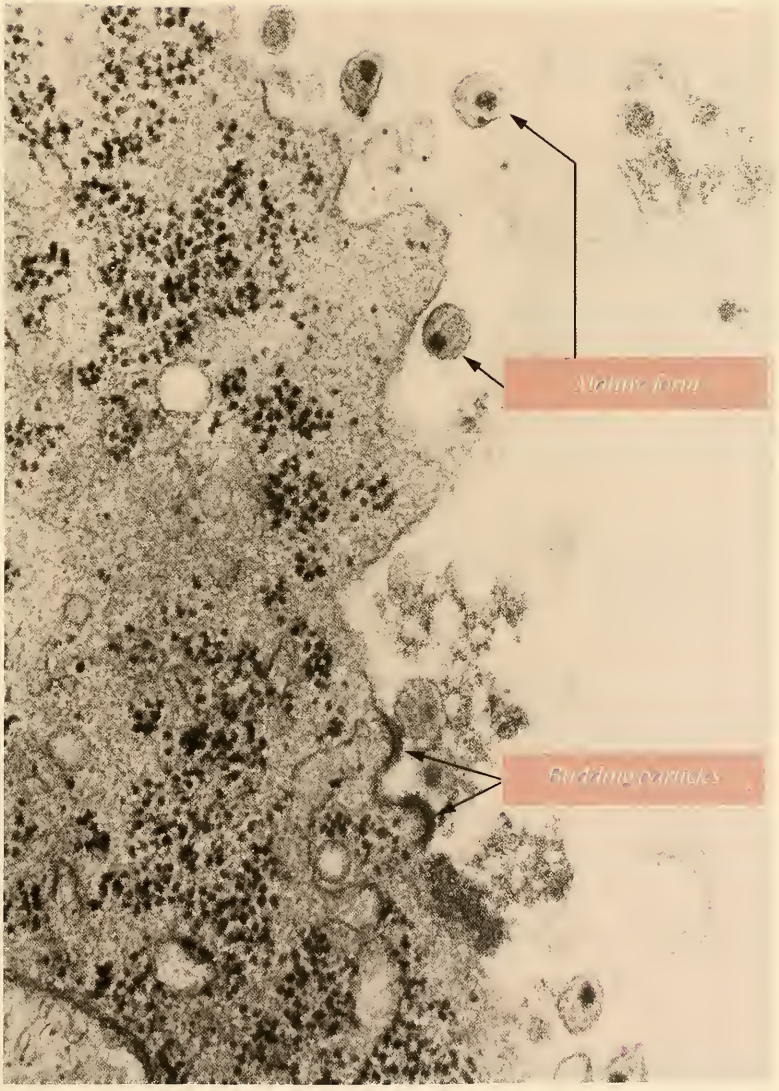
The Institute is involved with research on AIDS because about 1 percent of all patients with AIDS—approximately 165 patients as of July 1985—had no known risk factor, such as homosexuality or intravenous drug usage, but had received transfusions of blood or blood components within the past 5 years. In addition, approximately 73 patients receiving blood products to treat their hemophilia also contracted the disease. When one considers that between 3 and 4 million patients receive blood annually, it is not surprising that the NHLBI has been, along with other Institutes at the NIH, actively committed to meeting the challenge of this dread disease.

A significant advance occurred when scientists from the National Cancer Institute isolated a human T-cell lymphotropic virus (HTLV-III) from a number of patients with AIDS. HTLV-III is a retrovirus, which means that its genetic information is replicated from RNA rather than DNA. While there is no proof that HTLV-III causes AIDS, substantial data based on the isolation of the virus from AIDS patients and the detection of HTLV-III antibodies in their serum strongly support this hypothesis.

Because of the apparent causal relationship between HTLV-III and AIDS, the NHLBI responded swiftly by developing, implementing, and supporting several major programs. It supported research to establish tests to detect HTLV-III and is currently supporting efforts to evaluate such tests. Under another NHLBI-sponsored program, the first successful transmission of HTLV-III from humans to an animal species, the chimpanzee, has been accomplished. A contract has been awarded to study changes in immune function in transfused individuals in an effort to determine the relationship of these changes to the development of AIDS. The study will focus on immunologic changes in hemophilia patients, who are one of the high-risk groups for AIDS, and in heavily transfused blood recipients. This program is in its early stages, and results will be available only after a year or more of data collection.

The Institute has also initiated a program to collect serum samples from 200,000 blood donors in New York, San Francisco, Los Angeles, and Miami for eventual testing for HTLV-III antibodies. Later, recipients of blood and blood components from seropositive donors will be identified and evaluated. In the rapidly evolving field of AIDS research, the NHLBI will continue to work aggressively to solve the multifaceted problems posed by this disorder.

HTLV-III virus found in a hemophiliac patient



The Institute has the lead responsibility for research in sickle cell anemia and continues to support a variety of efforts designed to reduce morbidity and mortality in patients with this disorder. Activities to accomplish this objective include not only basic and clinical research, but also demonstration projects in diagnosis, counseling and patient management, and educational efforts directed to patients, the community, and medical and allied health professionals.

Scientists are pursuing studies to enhance our understanding of the structure and function of the sickle hemoglobin polymer, which appears to play a major role in the clinical expression of this disorder. Other investigators are exploring the role of the red cell membrane and factors affecting both decreased deformability of the red cell and increased adherence of the red cell to the inner lining of blood vessels. Knowledge of the mechanisms by which membrane properties are affected in this disease has important implications for understanding how sickled cells obstruct blood flow in the microcirculation and eventually lead to occlusion of vessels.

Of major interest is basic research to determine the effect of genetic modifiers, especially the control of fetal hemoglobin synthesis, on the clinical manifestations of sickle cell disease. Progress in this area has been due, in large part, to improved erythroid (red blood cell) culture techniques that permit study of cell differentiation during various stages of development. Basic and clinical research studies have validated the concept that it is possible to reverse the hemoglobin "switch" to favor increased production of fetal hemoglobin in patients with sickle cell disease and beta thalassemia. Unfortunately, the agents used to date have unacceptable side effects; therefore, investigators continue to search for less harmful compounds that augment fetal hemoglobin production. These efforts to stimulate fetal hemoglobin synthesis in patients with sickle cell disease, if achieved without an increase in intracellular hemoglobin concentration, would presumably be beneficial in treating this disease.

The technology used for mapping genes on chromosomes has allowed investigators to study the number of alpha globin genes in sickle cell disease patients. Patients inheriting three rather than the normal four genes controlling the alpha chain have mild alpha thalassemia, which is another inherited anemia; and such gene deletions have been reported to be beneficial in patients with sickle cell anemia, in that the anemia is less severe and there is a lower incidence of certain chronic complications. Other more controversial results of patients having both sickle cell anemia and alpha thalassemia have been suggested, such as greater life expectancy for these patients, but the findings remain to be confirmed.

Another development of clinical significance is the prenatal diagnosis of sickle cell disease, other hemoglobinopathies, chromosomal abnormalities, sex-linked disorders, and inborn errors of metabolism that depends on examining DNA from samples of chorionic villi (small vascular protrusions on the fetal membranes) obtained during the first trimester of pregnancy. This new method has distinct clinical, psychological, and laboratory advantages over the more widely used technique of prenatal and genetic analysis, which requires amniocentesis.

Investigators supported by NHLBI have also been exploring ways to deliver agents that inhibit sickling to various target sites. Specifically, they have found that a nontoxic carrier—phospholipid dispersions or liposomes—can deliver to the target site antisickling agents that are, by themselves, membrane-impermeable. *In vitro* results suggest that at least some of the damaging effects of sickling can be reduced or eliminated by this approach.

Research scientist working to further our understanding of sickle cell disease.

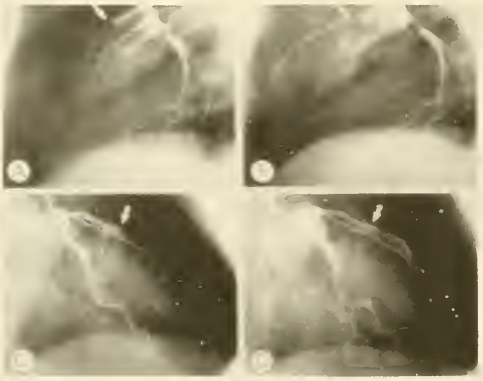
In the area of thrombosis, or blood clotting, NHLBI has multiple projects being supported at its Specialized Centers of Research (SCOR's) in thrombosis, in addition to the many other activities supported by traditional research project grants and program project grants. The Institute also collaborated in the establishment of a coagulation laboratory in a clinical trial on thrombolysis (clot dissolving) in myocardial infarction.

Recently, there have been two significant advances in the detection and localization of intravascular thrombi (clots in the blood vessels). The first is the production of a monoclonal antibody that binds to a small portion of fibrin, which is the essential portion of a blood clot. Unlike previous antibodies that have been produced, this one reacts only with fibrin and not with its precursor protein fibrinogen. Therefore, by radiolabeling this monoclonal antibody, blood clots can be more easily detected using conventional scanning techniques.

The second advance pertains to fragments E1—a portion of fibrin released by plasmin, which is an enzyme that breaks down clots. Researchers have demonstrated that fragment E1 also binds specifically to fibrin but not to fibrinogen, thereby leading to improved detection of blood clots through radiolabeling and scanning procedures.

Many complex biological factors related to thrombosis have been studied. In addition, research on platelets, which have a fundamental role in thrombosis, is also being pursued. In the related physiological process of breaking down or dissolving blood clots, scientists have made progress in the search for an effective and a safe thrombolytic agent. An enzyme has now been isolated from a cultured human kidney cell line. Animal studies have shown this enzyme, prourokinase, to be specific for a clot, safer, and more effective than urokinase, which is currently used to dissolve blood clots. When urokinase is used *in vivo*, it may also destroy fibrinogen, the compound in blood which is needed to form clots.

Another extremely promising agent for dissolving clots is tissue-type plasminogen activator, or t-PA. This substance converts plasminogen to plasmin in the body, normally after binding to fibrin clots. Thus, with t-PA, plasmin, an enzyme that breaks down clots, is concentrated at the site of a clot rather than spread throughout the circulatory system. Using recombinant DNA technology, scientists can now produce t-PA in sufficient quantities to test its clinical efficacy. Preliminary results from an NHLBI supported clinical trial are encouraging.



Thrombosis (clot dissolving) and reperfusion (blood flow) in coronary arteries before (A-C) and after (D-F) treatment with tissue-type plasminogen activator

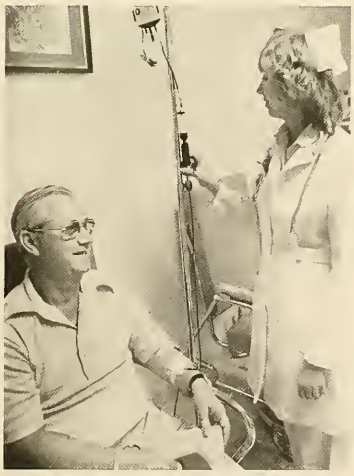
Overall, a major part of the effort to better understand thrombosis has been through an attempt to develop mechanisms for the study of the roles of soluble clotting factors and inhibitors, platelets and their secreted products, and the blood vessel wall in the hemostatic mechanism, and to explore the interactions among these components of the clotting system and other body defense systems. Researchers have developed and tested anticoagulants, platelet inhibitors, thrombolytic agents, and other modalities for the prevention and treatment of thromboembolic disorders.

The Institute is also working actively to obtain new knowledge of the function of platelets and their role in human pathophysiology. This includes improved diagnostic techniques related to platelet function, as well as a vital interest in seeing that platelet transfusions are employed only when specifically needed to provide hemostasis.

Transfusion Medicine

As a fundamental part of the effort to encourage appropriate and effective utilization of the Nation's blood resources, the NHLBI has initiated several programs in the special area of transfusion medicine. The NHLBI plans to establish SCOR's in transfusion medicine to foster basic and clinical research in this discipline. The NHLBI also hopes to establish a National Research and Demonstration Center (NRDC), which would help transfer new technologies and concepts in transfusion medicine into everyday application.

The NHLBI also initiated the Transfusion Medicine Academic Award in 1983. This award is designed to encourage medical schools, in cooperation with local blood centers, to develop curricula in transfusion medicine and to further the development of trained medical personnel who can serve the research and clinical needs of transfusion medicine. These efforts are extremely important in the overall management of the Nation's blood resources. Medical students of today are the teachers, researchers, and practitioners of tomorrow, and an early exposure to the best practices of tranfusion medicine will go a long way toward improving the understanding and techniques of the future generation of physicians in the field of transfusion medicine.



Patient receiving a blood transfusion. Through an expanded program of research grants, contracts, and academic awards, the NHLBI seeks to encourage basic and clinical research in transfusion medicine.

Epidemiology and Clinical Applications

Through epidemiological and clinical applications research, the Institute has made considerable progress in its mission to understand better and conquer diseases of the heart, lungs, and blood. Population-based research and research that promotes the transfer of technology from the laboratory bench to the bedside assist scientists in their efforts to evaluate the effectiveness of different therapies in reducing or preventing diseases within the Institute's mission. Scientists have also used such research to explore the relative importance of genetic and environmental risk factors as well as the impact of psychosocial or behavioral characteristics on heart, lung, and blood diseases. In recognition of the importance of a coordinated, ongoing program in these areas of research, NHLBI in 1984 established a separate Division of Epidemiology and Clinical Applications.

Much has been accomplished, but much remains to be done. Since it is not feasible to discuss so broad a program adequately in one section, the Council has chosen instead to focus briefly on five sample research projects in the areas of heart, lung, and blood diseases that show both the progress made in the past year and also the need for a continuing effort. These are only a few examples of NHLBI's effort in epidemiological and clinical applications research.

A participant in an Institute-supported clinical applications research project involving blood pressure and the elderly.

Mortality Rates and Trends in Coronary Heart Disease

In the Honolulu Heart Program, researchers are evaluating mortality rates and trends in coronary heart disease in men of Japanese ancestry living in Honolulu and then comparing the results with parallel data from men of Japanese ancestry in Japan and San Francisco. The impetus for this study was the observation that Japan has the lowest mortality rate from coronary heart disease in the world, but that Japanese who move to the United States appear rapidly to acquire coronary heart disease mortality rates characteristic of American Causacians. For the study, the researchers selected a cohort of 8,006 men of Japanese ancestry who were born in Japan or Hawaii between 1900 and 1919 and are presently living on the island of Oahu.

Results thus far have confirmed that the risk of coronary heart disease in Japanese men in Oahu, Hawaii, is approximately half that of Japanese men living on the U.S. mainland but about twice that of men living in Japan. The data were based on an evaluation of 18,000 serum samples, which were stored for future analysis, and 286 protocol autopsies. The major risk factors, which confirm those identified in the Institute's well-known Framingham Heart Study, include elevated blood pressure, smoking, elevated serum cholesterol, obesity, and glucose intolerance. Of those risk factors, the most significant are blood pressure and cigarette smoking. Other observations are that: complex carbohydrates in the diet and moderate alcohol intake appear to lower the risk for coronary heart disease; the amount of low density lipoproteins in the blood increases the risk for coronary heart disease, while the level of high density lipoproteins has the opposite effect; and the risk for hemorrhagic stroke increases as alcohol consumption increases.

These preliminary results suggest that environmental factors have a strong influence on coronary heart disease. By contrast, sociocultural-behavioral factors do not appear to be related to the incidence of coronary heart disease, cancer, or all-cause mortality.

These conclusions, however, are not definitive. The Honolulu Heart Program will be continued and expanded in scope in fiscal year 1985. In the cardiovascular area, the program will continue to involve: a thorough surveillance of morbidity and mortality rates of the cohort; an extensive analysis of risk factors associated with all forms of cardiovascular disease and a study of the prognosis after the onset of the disease; and an analysis of risk factors associated with anatomic pathology of the heart and great vessels, with a special emphasis on diet and psychosocial processes. But the study will also be expanded to include pulmonary function and respiratory diseases. In addition, the researchers will compare cardiovascular disease incidence and related risk factors of the Honolulu cohort with a similar group in Japan.

The Role of Inheritance and Environment in the Incidence of Cardiovascular and Pulmonary Diseases

Through the NHLBI Twin Study involving well over a thousand twins recruited from the twin registry maintained by the National Academy of Sciences, researchers propose to estimate the heritability of cardiovascular risk factors as well as to assess the roles of inheritance and environment in the incidence of cardiovascular and pulmonary diseases.

Results to date show a significant heritability for systolic and diastolic blood pressure, total blood cholesterol and low density lipoproteins, height, weight, uric acid, glucose, the expiratory volume of air that can be forcibly exhaled in 1 second, and heart rate. Some characteristics were not found to be heritable: the level of high density lipoproteins in the blood and forced vital capacity (a measurement of lung function). In future years, the researchers will concentrate on the incidence and prevalence of cardiovascular and pulmonary disease, and assess preclinical disease or signs of disease before symptoms are recognizable, to test whether the heritability of diseases exceeds what is expected based on known risk factors.

Prevention of Cardiovascular Disease in the Workplace

The purpose of this demonstration and education research project is to test whether successful methods used in other settings to reduce major cardiovascular disease risk factors can be adopted for use and be shown to be clinically and behaviorally effective in the workplace. Specifically, the study is based on the success of programs conducted in the workplace in controlling and reducing high blood pressure, especially among young and middle-age males. Several programs in the workplace have achieved control rates—defined as systolic blood pressure below 160 mm Hg and diastolic blood pressure below 95 mm Hg—from 68 percent to over 90 percent. This compares favorably with community control rates of 34 percent and even lower baseline rates in several employee populations surveyed under contract to NHLBI.

Display from the successful National Heart, Lung, and Blood Institute program for reducing high blood pressure in the workplace.

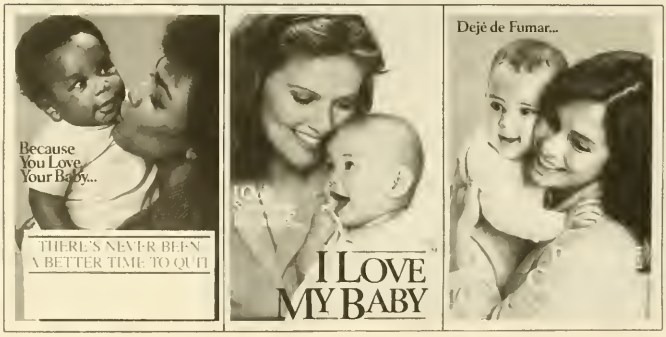
The Effect of "Passive Smoking" on Infants

Several studies in the United States and abroad have revealed that infants whose parents smoke have significantly more respiratory illness in their first year of life. But the effects of passive smoking on lung function of exposed children have been more difficult to document. Recently, the first longitudinal study of the effects of parental smoking concluded that children whose mothers smoked had a 7 percent reduction in their rate of lung growth compared to children of nonsmoking mothers. Results from two additional population studies also confirmed the finding of diminished lung function in children whose mothers smoke.

The long-term medical significance of these findings remains unknown, but to the extent that small decreases in pulmonary function persist, they may represent an important predictor of future respiratory problems, especially among those children who themselves become cigarette smokers. Long-term followup of children from homes where parents smoke and comparisons betweens studies will be necessary before this potentially important health issue can be resolved.

One of the problems encountered in conducting longitudinal studies on the effects of passive smoking was that only rough estimates of the individual's exposure to smoke has been available. These have been based on questionnaires regarding the number of smokers in the houshold. However, a more precise measure is now available. Researchers have developed a method that reliably measures the exposure of infants to second-hand cigarette smoke by measuring the amount of cotinine, a metabolite of nicotine, in the infant's urine. A pilot study has shown that infants in smoking households have significantly higher concentrations of nicotine and cotinine than infants not exposed to household smoke, Moreover, the greater the number of cigarettes the mother reported smoking, the higher the concentration of nicotine and cotinine in the infant's urine. In fact, some of the infants showed urinary and salivary concentration of nicotine an cotinine within the range found in some very light smokers.

This study is important for two reasons. First, it has shown that infants exposed to second-hand tobacco smoke actually absorb it. Second, the method developed can now be used to provide an objective measure of the amount of smoke absorbed by the infant, which can be used to study the short- and long-term health effects of passive smoking.



Institute sponsored research in the effects of "passive smoking" on infants strengthen[ed] the national "Because You Love Your Baby" program

Reexamination of Therapy for Cooley's Anemia

In Cooley's anemia, a genetically transmitted disease, patients cannot synthesize enough adult hemoglobin in their blood. This disease is usually treated by frequent transfusions of red blood cells, but the repeated transfusions cause toxic amounts of iron to build up in the tissues and heart. In order to slow down this iron overload, patients are given a drug called deferoxamine that ties up iron, thus lowering the rate of its deposit in the tissues. Preliminary data indicated that this therapy did not work well for patients who began treatment after the age of 10; those patients apparently developed serious cardiac problems.

These preliminary data have now been reexamined, and the results suggest that deferoxamine may be useful for patients of all ages. In a study of patients who used this drug consistently (12 hours per day, 5 days of every week) versus those who did not, cardiac disease occurred much less frequently in the group using deferoxamine. The researchers now plan to expand the scope of their epidemiological study. If the results are statistically significant in the larger study, this would be a dramatic finding confirming the value of this type of therapy in treating people of all ages suffering from Cooley's anemia.

A young adult with Cooley's anemia receiving deferoxamine therapy.

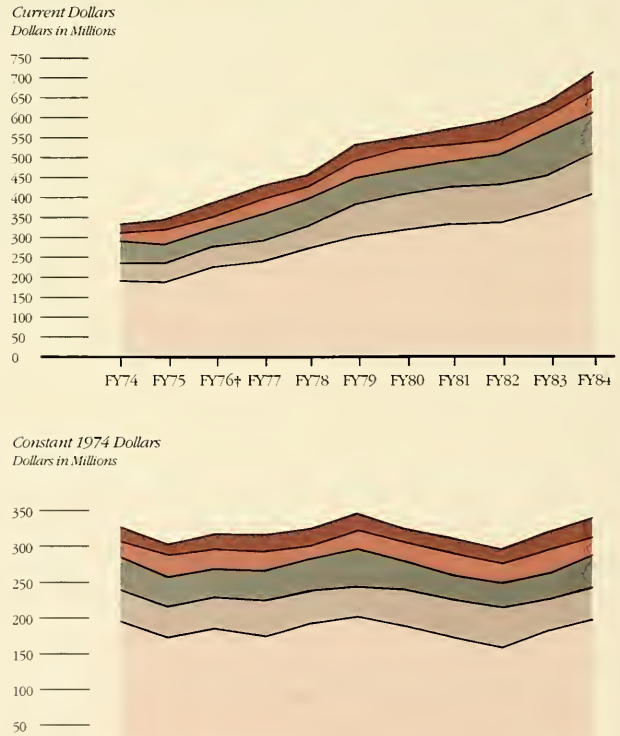
PRIORITIES, GOALS, AND RESOURCES

The Council is gratified to be able to report a significant downward trend in mortality from cardiovascular diseases, a trend that has persisted during 15 of the last 16 years. In the past 20 years, the mortality rate from coronary heart disease has decreased 39 percent and that from stroke 55 percent. And yet, the challenge still facing the National Heart, Lung, and Blood Institute is of staggering proportions. Diseases of the heart and blood vessels remain the number one killer of people in the United States, and diseases of the lung continue to escalate, with chronic obstructive lung disease the most rapidly rising cause of death in this country. Blood diseases also continue to take their toll; some, such as Cooley's anemia and sickle cell anemia, kill their victims early in their lives, while others contribute to cardiovascular and pulmonary disorders. Moreover, the incidence of transfusion-transmitted hepatitis is between 7 and 10 percent among the more than 3 million Americans who, during the year, received whole blood, red blood cells, platelets, or fresh-frozen plasma. And the total costs of cardiovascular, lung, and blood diseases in our Nation has been estimated at more than $120 billion.

Basic research, which is the focus of this Council report, continues to provide the major tools for meeting and, we hope, ultimately conquering these immense problems. Thus, in December 1983, the Institute initiated a series of symposia called "Frontiers in Basic Sciences that Relate to Heart, Lung, and Blood Diseases." The symposia are designed to identify the research areas of biological interest that are ready for application to the study of heart, lung, and blood diseases. The December 1984 conference, for example, emphasized the characteristics of the plasma membrane and its role as a site for receptors involved in physiological regulation of the cardiovascular, pulmonary, and blood systems. These conferences, which have brought together basic researchers and clinicians, have been enthusiastically received by the biomedical research community and have stimulated new initiatives in the area of heart, lung, and blood diseases.

Of the problems facing the Institute, undoubtedly the most critical is how, with limited resources, to maintain the momentum of the exciting advances in basic research, the various clinical applications of research, and the necessary balance between the heart, lung, and blood programs. Great scientific opportunities exist to control the devastating diseases of the heart, lungs, and blood, but adequate research funding is necessary. As shown in the figure "NHLBI Obligations," although the Institute has apparently received a substantial increase in its funding capabilities over the past decade, the actual increase, when adjusted for inflation, is negligible. Thus, the current dollars show a significant increase of $378.8 million, from $326.3 million in FY 1974 to $705.1 million in FY 1984; however, the constant dollars (purchasing power) had gone up only $10.3 million

NHLBI Obligations: Fiscal Years 1974-1984*

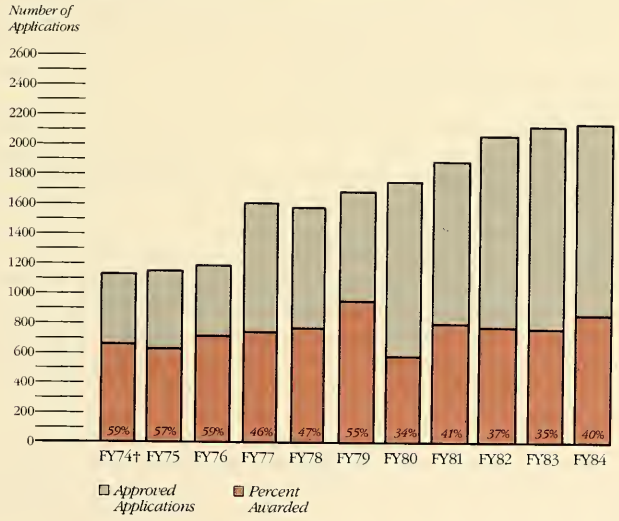


* *Excludes General Research FY 1974*
† *Excludes Transition Quarter*

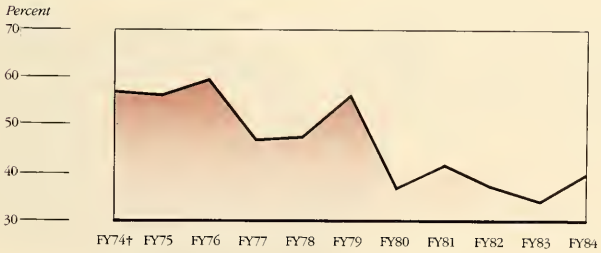
by FY 1984. In fact, 5 years ago, in FY 1979, the situation in terms of constant dollars was better by $5 million. In FY 1984, of the 2,119 applications that were approved—judged by peer reviewers to be of sufficient merit to be worthy of support—only 852 were funded. The funding rate was 40 percent, which compares unfavorably with a funding rate of almost 60 percent in FY 1974. During FY 1984, many worthwhile projects could not be funded, projects with the potential for leading to discoveries that could improve the health of the American people.

In the following section, the Council will describe several Institute priorities in the immediate future.

NHLBI Competing Research Project Grants: Applications Reviewed, Approval Recommended, and Awarded, Fiscal Years 1974-1984*



NHLBI Competing Research Project Grants: Percent Funded, Fiscal Years 1974-1984



* *Includes R01, R23, P01, R43 grants (R43 grants beginning in Fiscal Year 1983).*
† *Reflects release of fiscal year 1973 impounded funds.*
Source: *Division of Research Grants, NIH.*

The Institute continues to foster and issue solicitations for SCOR's. The NHLBI and the Council believe that the multidisciplinary nature of individual SCOR's when combined with the program emphasis on coordination among the center grantees provide the Institute with a valuable mechanism of support. Centers are an effective means of concentrating resources, facilities, and personnel on specific high priority research topics in the areas of heart, lung, and blood diseases and blood resources. Within each SCOR program is a coordinated network of multidisciplinary research centers. These centers maintain a close interaction among the individual investigators and with the Institute while working independently on separate but related research topics within each SCOR program area. The research at each of the centers includes both a basic science and clinical emphasis, to ensure that basic advances are rapidly translated into clinical applications and also that clinical needs provide a direction for the basic science.

The SCOR program has been an important part of the Institute since 1970, when the Institute announced a competition to award support for a limited number of research centers devoted to the solution of high priority problems related to arteriosclerosis, hypertension, pulmonary disease, and thrombosis. The Institute's intent in establishing the centers was to expedite the development and application of new knowledge essential for improved diagnosis, treatment, and prevention of the disease areas under the NHLBI purview.

Since the inception of the SCOR's, there have been active programs in each of the major program areas of the Institute. In FY 1971 (the first year of SCOR program operation), 34 centers were established. Beginning in FY 1984 a new dimension was added to the program. On the advice of a working group of the National Heart, Lung, and Blood Advisory Council, the Institute reformulated its congressionally mandated National Research and Demonstration Centers (NRDC) program. SCOR's are being offered the opportunity to enhance their basic and clinical research by adding one or more thematically related projects in demonstration and education research. Competitions for NRDC and SCOR enhancement awards were announced in FY 1984 for the hypertension, ischemic heart disease, arteriosclerosis, and thrombosis programs. In addition, the Institute would like to initiate two new SCOR programs in the near future that would focus upon transfusion medicine and childhood heart disease.

The extensive system of scientific reviews imposed on SCOR programs ensures that they continue to produce high quality research. But despite satisfaction with the SCOR concept and its expansion since 1970, the percentage of the NHLBI budget resources committed to the SCOR programs has been virtually constant. From FY 1975 through FY 1984, the SCOR programs remained at less than 9 percent of the NHLBI budget. In FY 1985, the Institute is supporting 47 SCOR's: 22 in the heart and vascular diseases program; 21 in the lung diseases program; and 4 in blood diseases and blood resources program. (In addition, there are 10 Comprehensive Sickle Cell Centers.)

The National Heart, Lung, and Blood Advisory Council believes that a substantial return on the investment in SCOR programs has already been realized. While SCOR subject areas may change, the concept will continue to be valuable. No other existing support mechanism offers the advantages of a coordinated, multidisciplinary network in targeting basic and clinical research on major national health problems.

Specialized Centers of Research (SCORs)

Adult Respiratory Failure
- Massachusetts General Hospital, Boston, Mass.
- St. Louis University, St. Louis, Mo.
- University of California, San Diego, La Jolla, Calif.
- University of Texas, San Antonio, Tex.
- University of Washington, Seattle, Wash.

Arteriosclerosis
- Baylor College of Medicine, Houston, Tex.
- Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, N.C.
- Columbia University, New York, N.Y.
- Louisiana State University, Baton Rouge, La.
- University of California, San Diego, La Jolla, Calif.
- University of California, San Francisco, Calif.
- University of Chicago, Chicago, Ill.
- University of Iowa, Iowa City, Iowa

Chronic Airway Diseases
- Harvard University, Boston, Mass.
- University of Arizona, Tucson, Ariz.

Hypertension
- Boston University, Boston, Mass.
- Cornell University Medical School, New York, N.Y.
- University of Alabama, Birmingham, Ala.
- University of California, San Diego, La Jolla, Calif.
- Vanderbilt University School of Medicine, Nashville, Tenn.

Ischemic Heart Disease
- Cedars-Sinai Medical Center, Los Angeles, Calif.
- Duke University, Durham, N.C.
- Harvard Medical School, Boston, Mass.
- Johns Hopkins University, Baltimore, Md.
- University of Alabama, Birmingham, Ala.
- University of California, San Diego, La Jolla, Calif.
- University of Iowa, Iowa City, Iowa
- University of Texas, Southwestern Medical School, Dallas, Tex.
- Washington University, St. Louis, Mo.

Occupational and Immunologic Lung Diseases
- National Jewish Hospital and Research Center, Denver, Colo.
- Tulane University, New Orleans, La.
- University of Vermont, Burlington, Vt.

Pediatric Pulmonary Diseases
- Boston Hospital for Women, Boston, Mass.
- Columbia University, College of Physicians and Surgeons, New York, N.Y.
- University of California, San Francisco, Calif.
- University of Minnesota, Minneapolis-St. Paul, Minn.
- University of North Carolina, Chapel Hill, N.C.
- University of Washington, Seattle, Wash.
- University of Wisconsin, Madison, Wis.
- Vanderbilt University School of Medicine, Nashville, Tenn.

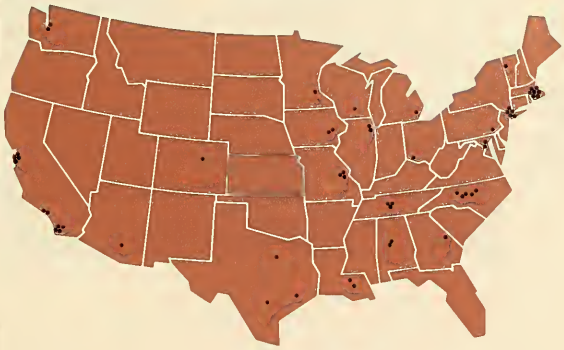
Pulmonary Vascular Diseases
- Children's Hospital Medical Center, Boston, Mass.
- University of California, San Francisco, Calif.
- Vanderbilt University, Nashville, Tenn.

Thrombosis
- Cornell University Medical School, New York, N.Y.
- Temple University School of Medicine, Philadelphia, Pa.
- University of North Carolina, Chapel Hill, N.C.
- Washington University, St. Louis, Mo.

Comprehensive Sickle Cell Centers

- Boston City Hospital, Boston, Mass.
- Children's Hospital, Cincinnati, Ohio
- Columbia University, College of Physicians and Surgeons, New York, N.Y.
- Duke University, Durham, N.C.
- Howard University College of Medicine, Washington, D.C.
- Medical College of Georgia, Augusta, Ga.
- University of California, San Francisco, Calif.
- University of Illinois, Chicago, Ill.
- University of Southern California School of Medicine, Los Angeles, Calif.
- Wayne State University, Detroit, Mich.

Location of NHLBI-Supported Centers (FY 1984)



Technological Innovations Through the Small Business Innovation Research Program

Several developments have increased the interactions between government agencies and commercial organizations to promote improvements in the health of the Nation. The Small Business Innovation Development Act of 1982 (P.L. 97-219), which authorized the Small Business Innovation Research (SBIR) Program, requires Federal research and development (R&D) agencies to set aside a portion of their extramural budget for the SBIR program. The goals of the SBIR program are to stimulate technological innovation within the small business community, to provide small businesses with an increased role in Federal research and development, and, by attracting private capital, to commercialize the results of federally funded research. In administering the act, a small business is defined as an organization independently owned and operated for profit, not dominant in the field in which it is operating, and having 500 or fewer employees.

The SBIR program consists of three separate phases. Phase I, which is approximately 6 months duration, is to establish the technical merit and feasibility of R&D ideas that may lead ultimately to commercial products or services in the health area. Phase II funding, which is based on the results of phase I and on the scientific and technical merit of the phase II application, lasts for approximately 2 years, and is a continuation of the R&D efforts initiated in phase I. Phase III enables the small business to pursue with non-Federal funds the commercialization of the results of phases I and II funding.

In FY 1983, the NHLBI awarded its first SBIR grants from set-aside funds. In FY 1984, the amount was 0.7 percent of the Institute's total research grant dollars. The SBIR set-aside will reach 1.0 percent in FY 1985. The Council believes that these SBIR awards should not interfere with the other grant programs of the Institute.

Career Development

The Council has a longstanding commitment to support research training and career development, for we believe that the investment in trained biomedical investigators is among the most critical priorities for the continued advance against heart, lung, and blood diseases. The Council remains especially concerned over the problems of attracting physicians into a career in research.

As an incentive, the NIH developed the Physician Scientist Award to enable physicians with clinical training to have up to 5 years of special study in basic science along with a supervised research experience. The Physician Scientist Award is helping support the transition of a physician from clinical training status to that of a productive investigator able to compete successfully for NIH research support. The first phase of the program (2 to 3 years) includes both study and laboratory experience supervised by an individual with extensive research experience in the fundamental sciences. The second phase (up to 3 years) applies laboratory-based research in either a basic science or clinical department.

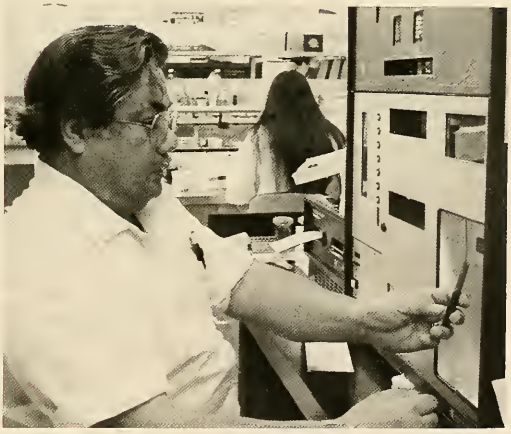
Funds for the program were first awarded in FY 1984. Based on the initial strong success of this award, but also on the need to further encourage physicians to become independent investigators, the NHLBI initiated a competitive extension of the Physician Scientist and Clinical Investigator Awards. This change, which was originally proposed by the Council, will allow awardees to apply for an additional 3 years of support.

Recent data indicate that members of minority groups are not well represented in the population of Ph.D. biomedical scientists. Although 12 percent of the population is black, less than 0.25 percent of persons holding a Ph.D. in science are black. The percentages are even smaller for Ph.D.'s in the biomedical sciences who are black.

To address this problem, the NHLBI announced the Minority School Faculty Development Award, which will encourage the development of faculty investigators at minority schools in areas relevant to cardiovascular, pulmonary, or blood diseases, and the Minority Institutional Research Program, which will train graduate students in minority schools for research careers related to heart, lung, or blood diseases. The two new programs follow the establishment of a Minority Summer Program in Pulmonary Research, which was designed to provide opportunities for minority school faculty members and graduate students to gain experience and exposure to ongoing pulmonary research projects at established pulmonary training centers.

Construction and Renovation of Facilities

The Council has often expressed its concern about the lack of adequate physical and laboratory resources for heart, lung, and blood research and recommended support for the construction of research facilities for NHLBI-supported programs. In December 1984, the Institute announced a grant program to support the improvement, renovation, and establishment of modern research facilities throughout the Nation, to be shared by investigators who will make use of advances in biomedical sciences, such as molecular biology. The purpose of the program is to expand or create facilities that enable investigators to apply newly developed, modern, sophisticated technology to fundamental research on heart, lung, and blood diseases. The Council supports this program and would like to see it expanded in future years.



Minority research scientists. Special NHLBI programs and awards are designed to increase the representation of such scientists in the biomedical research community.

Budget Recommendations

The National Heart, Lung, and Blood Advisory Council is firmly committed to a balanced and diverse program of biomedical research and training for the benefit of the public health. Such a program makes use of a variety of support mechanisms, including investigator-initiated research as well as program project grants, institute-initiated research and center grants, and contracts. The program includes basic as well as applied and clinical research, laboratory and clinical trials, fundamental studies of biologic phenomena, and demonstration and education activities.

In recommending the budgets for FY 1987 through FY 1991, the Council reaffirms these principles for the determination of funding levels:

- Budgets must increase to keep pace with increasing costs of doing research.
- At least one-third of all uncommitted funds each year should be used for centers, contracts, training, career awards, and other research mechanisms that make up a balanced Institute program, with the remaining two-thirds available for regular grants and program project grants.
- Resources should be sufficient to fund 50 percent of all approved applications for research grants.

Using these principles and assuming a 5 percent inflation rate, the Advisory Council offers the following two sets of budget figures for FY 1987 through FY 1991. The first set shows the minimum amounts needed for the NHLBI to maintain its current level of funding:

FY 1987	FY 1988	FY 1989	FY 1990	FY 1991
950.3M	*997.8M*	*1,047.0M*	*1,100.0M*	*1,155.0M*

The Council, however believes that the current level of funding is inadequate for the Institute to develop its initiatives in such priority areas as the SCOR program, career development of researchers, especially physician scientists and minority scientists, and construction and renovation of research facilities. In addition, with the current low funding rate for grant applications, many promising research projects in all areas remain unfunded. Therefore, the Council strongly recommends the following budget:

FY 1987	FY 1988	FY 1989	FY 1990	FY 1991
1,052.1M	*1,104.7M*	*1,159.9M*	*1,217.9M*	*1,278.8M*

Credits

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